EXHIBIT 1

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte EEVA-MARJA RUTANEN

Appeal 2009-001910
Application 11/048,685
Technology Center 1600

Decided: August 4, 2009

Before DEMETRA J. MILLS, ERIC GRIMES, and RICHARD M. LEBOVITZ, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

STATEMENT OF CASE

This is an appeal under 35 U.S.C. § 134. We have jurisdiction under 35 U.S.C. § 6(b).

The following claim is representative.

1. A method for identifying a patient with intact foetal membranes possessing risk factors indicative of preterm delivery comprising:

a) detecting a level of IGFBP-1 in an essentially blood-free vaginal or cervical secretion sample from said patient with an antibody that recognizes IGFBP-1;
b) comparing said level of IGFBP-1 to a high level of 100 µg/l and a low level of less than 1.0 µg/l;
c) identifying a level of IGFBP-1 that is less than 100 µg/l and equal to or greater than 1 µg/l; and
d) providing medical advice designed to prevent preterm delivery to said patient where said sample has an IGFBP-1 level that is less than 100 µg/l and equal to or greater than 1 µg/l, wherein said level of IGFBP-1 being less than 100 µg/l and equal to or greater than 1 µg/l, despite intact foetal membranes, indicates that said patient possesses risk factors indicative of preterm delivery, said risk factor of said patient being increased as compared to patients with an IGFBP-1 level of less than 1 µg/µl [sic].

CITED REFERENCES

Senyei	US 5,096,830	Mar. 17, 1992
Konstantinov	US 5,597,700	Jan. 28, 1997
Rutanen	WO 92/12426	July 23, 1992
Rutanen'99	WO 99/58974	Nov. 18, 1999

Eeva-Marja Rutanen et al., "Diagnosis Of Premature Rupture Of Fetal Membranes By The Measurment Of Insulin-Like Growth Factor Binding Protein-1 In Cervical Secretion," *Department of Obstetrics and Gynecology*, University Central Hospital, and Minerva Institute for Medical Research, 38, Helsinki Finland.

Charles J. Lockwood et al., "Fetal Fibronectin In Cervical And Vaginal Secretions As A Predictor Of Preterm Delivery," 325 (10) *The New England Journal of Medicine* 669-674 (1991).

Eeva-Marja Rutanen et al., "Measurement of insulin-like growth factor binding protein-1 in cervical/vaginal secretions: comparison with the ROM-check Membrane Immunoassay in the diagnosis of ruptured fetal membranes," 214 *Clinica Chimica Acta* 73-81 (1993).

Melissa Westwood et al., "The Phosphorylation Pattern of Insulin-Like Growth Factor-Binding Protein-1 in Normal Plasma Is Different from That

in Amniotic Fluid and Changes during Pregnancy," 79 (6) *Journal of Clinical Endocrinology and Metabolism*, 1735-1741 (1994).

Charles J. Lockwood, MD. et al. "Fetal membrane rupture is associated with the presence of insulin-like growth factor-binding protein-1 in vaginal secretions," 171 (1) *Am. J. Obstet. Gynecol.* 146-149 (July 1994).

Eeva-Marja Rutanen et al., "Evaluation of a rapid strip test for insulin-like growth factor binding protein-1 in the diagnosis of ruptured fetal membranes," 253 *Clinica Chimica Acta*, 91-101 (1996).

GROUNDS OF REJECTION

1. Claims 1, 3-6, 13, 15-18, 25, and 26 are rejected under 35 U.S.C. § 112, first paragraph for lack of written description.

2. Claims 1, 3-7, 9-13, 15-19, and 21-26 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

3. Claims 1, 3-7, 9-13, 15-19, and 21-26 are rejected under 35 U.S.C. § 112, second paragraph for claim indefiniteness.

4. Claims 26 is rejected under 35 U.S.C. § 102(b) over Rutanen 1991.

5. Claims 1, 3-7, 9-12, 19, and 21-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rutanen (1991) in view of Senyei.

Written Description

1. Claims 1, 3-6, 13, 15-18, 25, and 26 are rejected under 35 U.S.C. § 112, first paragraph for lack of written description.

ISSUE

The Examiner finds that there is

> no written description or support for the invention as is now claimed wherein those patients determined to have

> "intermediate" levels of insulin-like growth factor binding protein 1 (IGFBP- 1) above baseline and below that indicative of membrane rupture, that is those patients alleged to have a mature cervix, are advised or treated to prevent pre-term delivery because the [S]pecification teaches against an expectation of success in treating such patients (i.e. considerable changes have already taken place in the cervix and delivery is impending).

(Ans. 7.)

Appellant contends that there is written descriptive support in the Specification, referencing specific locations in the Specification, for the Appellant's claimed invention. (App. Br. 11-17.)

The Issue is: Has Appellant demonstrated error in the Examiner's finding that the Specification does not describe advising patients to prevent pre-term delivery?

PRINCIPLES OF LAW

"The 'written description' requirement . . . serves both to satisfy the inventor's obligation to disclose the technologic knowledge upon which the patent is based, and to demonstrate that the patentee was in possession of the invention that is claimed. . . . The descriptive text needed to meet these requirements varies with the nature and scope of the invention at issue, and with the scientific and technologic knowledge already in existence." *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). "It is not necessary that every permutation within a generally operable invention be effective in order for an inventor to obtain a generic claim, provided that the effect is sufficiently demonstrated to characterize a generic invention." *Id.* at 1359.

FINDINGS OF FACT

> 1. According to the inventor's observations, the concentration of IGFBP-1 in vaginal or cervical secretions can be elevated even when the foetal membranes are intact. However, in a sample extracted in 0.5 ml of a buffer, the IGFBP-1 concentration does not exceed about 100 µg/l, unless it originates from amniotic fluid resulting from ruptured foetal membranes. This finding has brought to light the fact that, when the foetal membranes remain intact, this slight but higher than baseline elevation can be interpreted as protein leaking directly from decidual cells. If the sample contains amniotic fluid, the test based on the invention cannot be used to show elevation of the IGFBP-1 level due to leaking decidual cells, since the concentration of IGFBP-1 due to the presence of amniotic fluid is higher.

(Spec. 12.)

2. "Table 3 shows that, as spontaneous delivery approached in women whose membranes were still intact, the concentration of IGFBP-1 in the extracted sample varied between about 1 and 61 µg/l. Higher concentrations of IGFBP-1 (8100, 6160 µ/l [sic, µg/l]) associated with ruptured foetal membranes are clearly distinguishable." (Spec. 15.)

3. The Specification states that, "[c]oncentrations [of IGFBP-1] above the baseline level indicate the presence of some active process. This, together with clinical information, is used to decide whether any treatment is necessary." (*Id.*)

4. The Declaration of Mika Nuutila testifies to the use of Dr. Rutanen's invention in the course of practicing medicine and that "Dr. Rutanen's invention has provided useful results in the diagnosis and treatment of pregnant women at risk of preterm delivery." (Declaration, page 2.)

5. Appellant relies on the Declaration of Jorma Paavonen explaining that one of ordinary skill in the art reading the Specification would

understand that it explains the invention now claimed. (Br. 17; Declaration Paavonen, pages 2-4.)

ANALYSIS

The Examiner finds that there is no written description or support for the invention as is now claimed because the Specification teaches against an expectation of success in treating patients with intermediate levels of IGFBP-1 and at risk of preterm delivery as claimed because "considerable changes have already taken place in the cervix and delivery is impending." (Ans. 7.)

We are not persuaded by the Examiner's finding. Appellant claims a method for identifying a patient with intact foetal membranes possessing risk factors indicative of preterm delivery. The claim does not require prevention of preterm delivery as alleged by the Examiner. The claim requires in step (d), "providing medical advice designed to prevent preterm delivery." Thus, no particular expectation of success of prevention of preterm delivery is required by the claim as argued by the Examiner.

It would reasonably appear from the facts of record (FF1-5) that the Specification describes the method as claimed.

CONCLUSION OF LAW

Appellant has demonstrated error in the Examiner's finding that the Specification does not describe advising patients to prevent pre-term delivery. The written description rejection is reversed.

Enablement

2. Claims 1, 3-7, 9-13, 15-19, and 21-26 are rejected under 35 U.S.C. § 112, first paragraph for lack of enablement.

ISSUE

> The Examiner argues that the Specification is not enabling for
>
> a method of determination of insulin-like growth factor binding protein 1 (IGFBP- 1) as indicative of susceptibility to preterm or impending delivery, and/or maturity of the cervix, or risk of preterm labor, or for any indication other than the known indication of fetal membrane rupture. There is nothing in evidence which would allow one to determine cervical ripeness (i.e. maturity) or other delivery indications, and to exclude the presence of amniotic fluid, on the basis of the disclosed and instantly claimed methods alone.

(Ans. 8.)

The Examiner argues that "Appellant has provided no nexus believable to one of skill in the art between 'intermediate' levels of IGFBP-1 (i.e. instantly disclosed and claimed as less than the 100 µg/l level selected, in order to limit the detection of false positives (page 12; see also Rutanen et al., 1993), as indicative of fetal membrane rupture." (Answer 9.) The Examiner argues that "the source and significance of the instant 'intermediate' levels of detectable IGFBP-1 in cervical or vaginal secretions (also referred to herein as cervicovaginal secretions) would seem to be unknown and unpredictable for a variety of reasons, particularly in 1992." (*Id.*)

The issue is: Has Appellant demonstrated that the Examiner erred in concluding that the Specification is not enabling to practice the claimed invention?

PRINCIPLES OF LAW

As explained in *In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1995), the USPTO should not confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption," citing *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994). See *In re Anthony*, 414 F.2d 1383, 1395 (CCPA 1969)("Congress has given the responsibility to the FDA[1], not to the [PTO], to determine . . . whether drugs are sufficiently safe"). This logic would similarly apply to diagnostic medical devices.

Patentability determinations are based on a preponderance of the evidence. "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." *In re Oetiker*, 977 F.2d 1443, 1445 (Fed. Cir. 1992).

FINDINGS OF FACT

6. The Specification page 15, Table 3, evidences that there is a population of pregnant women patients with intact and unruptured foetal membranes with a level of IGFBP-1 that is less than 100 µg/l and equal

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[1] The Federal Food, Drug, and Cosmetic Act (FD&C Act) gives FDA broad authority to regulate medical devices, which are defined in part as any "in vitro reagent or other related article, including any component, part, or accessory, which is . . . intended for use in the diagnosis of disease." 21 U.S.C. § 321(h) (2005).

to or greater than 1 μg/l, that is at risk of preterm delivery and may require medical advice different from a patient having preterm contractions but an IGFBP-1 level that is less than 1 μg/l.

7. According to the Specification, page 3, some 80 to 90% of patients having preterm contractions, require no intervention, however from 10-20% of pregnant women having preterm contractions require some form of medical advice or intervention to delay or prevent preterm delivery.

8. Lockwood 1994 suggests that a level of IGFBP-1 of greater than 3 μg/l is indicative of foetal membrane rupture (Ans. 13)

9. Rutanen 1996 mentions IGFBP-1 levels of 25 μg/l is indicative of foetal membrane rupture. (Ans. 13.)

ANALYSIS

We are not persuaded by the Examiner's reasoning. The Specification page 15, Table 3, evidences that there is a population of pregnant women patients with intact and unruptured foetal membranes with a level of IGFBP-1 that is less than 100 μg/l and equal to or greater than 1 μg/l, that is at risk of preterm delivery and may require medical advice different from a patient having preterm contractions but an IGFBP-1 level that is less than 1 μg/l. According to the Specification, page 3, some 80 to 90% of patients having preterm contractions require no intervention, however from 10-20% of pregnant women having preterm contractions require some form of medical advice or intervention to delay or prevent preterm delivery. Dr. Mika Nuutila, a physician, testifies that the claimed diagnostic testing is effective. (FF 4.)

While we acknowledge that Lockwood 1994 suggests that a level of IGFBP-1 of greater than 3 μg/l is indicative of foetal membrane rupture

(Ans. 13) and Rutanen 1996 mentions IGFBP-1 levels of 25 µg/l is indicative of foetal membrane rupture, the claimed method as defined in its preamble involves those patients with the claimed IGFBP-1 level whose membranes are not ruptured. The weight of the evidence supports the position of Appellant, and the enablement rejection is reversed.

CONCLUSION OF LAW

Appellant has demonstrated that the Examiner erred in concluding that the Specification is not enabling to practice the claimed invention.

Indefiniteness

Claims 1, 3-7, 9-13, 15-19, and 21-26

Claims 1, 3-7, 9-13, 15-19, and 21-26 are rejected under 35 U.S.C. § 112, second paragraph for claim indefiniteness.

The Examiner argues that the claimed method steps are unclear because there is no connection between the sample level in step (a) and the identified level in step (c). (Ans. 15.)

PRINCIPLES OF LAW

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification." *Miles Laboratories, Inc. v. Shandon, Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993). Claims are in compliance with 35 U.S.C. § 112, second paragraph, if "the claims, read in light of the [S]pecification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits." *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1385 (Fed. Cir. 1986).

ANALYSIS

We conclude that one skilled in the art would understand the bounds of the claim when read in light of the Specification. In our view, one of ordinary skill in the art reading the claimed method would understand that a level of IGFBP-1 in an essentially blood-free vaginal or cervical secretion sample is detected and that value is compared to a level of IGFBP-1 to a high level of 100 µg/l and a low level of less than 1.0 µg/l. If the detection identifies a level of IGFBP-1 that is less than 100 µg/l and equal to or greater than 1 µg/l then medical advice is given. The indefiniteness rejection of claims 1, 3-7, 9-13, 15-19, and 21-26 is reversed.

Claims 13 and 15-18

The Examiner concludes that claims 13 and 15-18 are unclear as to what is intended by the phrase "intact maturation of the lower." (Ans. 15.) Appellant acknowledges that the term "membranes" was inadvertently deleted from claim 13. (App. Br. 22.) Therefore, we affirm the rejection of claims 13 and 15-18.

Anticipation

Claims 26 is rejected under 35 U.S.C. § 102(b) over Rutanen 1991.

ISSUE

The Examiner finds that:

> With sandwich immunoassays using two monoclonal antibodies, one of which being implicitly labeled, Rutanen et al. detected levels of IGFBP-1 in swabbed samples of cervical secretions in various ranges: undetectable in nonpregnant patients; a range of from undetectable to detectable up to 90 ng/ml (i.e. 90 µg/l) in pregnant patients with apparently intact fetal membranes; and an increased level ranging from 175 to 20,000 ng/ml (i.e. µg/l) in pregnant patients implicitly

> highly susceptible to delivery due to rupture of fetal membranes. Rutanen et al. implicitly teach comparisons among detected ranges of IGFBP-1 levels, pregnancy status, and fetal membrane status, implicitly identifying the samples in each range. ... Providing medical advice to a patient regarding the ranges of detected IGFBP-1 levels, pregnancy status, fetal membrane status, and a safe, full-term, delivery would have been implicit in the medical care of pregnant patients.

(Ans. 16.)

Appellant contends that

> [b]ecause Rutanen et al. (1991) publication teaches only a binary, high-low IGFBP-1 concentration level in cervical samples taken from pregnant women for diagnosing ruptured foetal membranes, it fails to expressly anticipate the presently claimed method for detecting an intermediate IGFBP-1 concentration range in vaginal/cervical samples for diagnosing a risk for pre-term delivery recited in claim 26. Because, in view of the teachings of Rutanen et al. (1991), there is no necessity that intermediate IGFBP-1 concentrations be correlated with a detached state of foetal membranes indicative of a risk for pre-term delivery, the Rutanen et al. (1991) publication cannot inherently anticipate the present claims.

(App. Br. 25.)

The issue is: Has Appellant demonstrated error in the Examiner's anticipation rejection?

FACT AND ANALYSIS

We find Appellant's arguments convincing. Rutanen 1991 does not specifically attribute any significance to the claimed values of IGFBP-1 in a patient with intact foetal membranes and a risk of preterm delivery, and therefore does not teach the claimed step of "d) providing medical advice designed to prevent preterm delivery to said patient where said sample has

an IGFBP-1 level that is less than 100 µg/l and equal to or greater than 1 µg/l."

CONCLUSION OF LAW

Appellant has demonstrated error in the Examiner's anticipation rejection.

OBVIOUSNESS

Claims 1, 3-7, 9-12, 19, and 21-26 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Rutanen (1991) in view of Senyei.

ISSUE

According to the Examiner the "teachings of Rutanen et al. (1991) differ from the invention as instantly disclosed and/or claimed in not teaching extraction of the sample from the swab and in not teaching the ranges of IGFBP-1 levels as instantly claimed." (Ans. 18.)

The Examiner concludes that it "would have been obvious to one of ordinary skill in the art at the time the instant invention was made to have extracted a cervicovaginal secretion sample from the swab used for its collection prior to performance of the immunoassay of Rutanen et al. (1991) because Senyei et al. teach that this step is conventional." (Ans. 18.)

We do not find that Senyei overcomes the deficiencies of Rutanen 1991 as discussed above, and the rejection of the claims for obviousness is reversed.

SUMMARY

All rejections are reversed except for the rejection of claims 13 and 15-18 for claim indefiniteness, which is affirmed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a).

AFFIRMED IN PART

REVERSED IN PART

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